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NEURAL-EPITHELIAL INTERACTIONS IN SENSORY RECEPTORS

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The specific types of relationships that exist between sensory nerve fibers and the associated epithelial cells have been reviewed in a variety of sensory systems. In many sensory systems, perhaps most, specificity of terminal epithelial element provides a degree of specificity to the cytologic pattern of the terminal receptor. We can see examples of such interaction, not only in the case of intraepithelial nerve fibers where nerves tend to be associated with Merkel cells, but also in the case of corpuscular receptors, both of these being examples of mechanosensory systems. Equivalent types of specificity are present within the special senses, where a specific receptor cell can be described. These findings strongly suggest that specificity in the peripheral nervous system is the rule rather than the exception, a thesis proposed over a hundred years ago by F. Merkel.

How do sensory nerve fibers and epithelial cells interact in specific sensory receptors? For the sake of argument, let us consider F. Merkel's thesis of almost a century ago. In his monograph [1] on the nature of sensory nerve endings in skin, Merkel reviewed the sensory terminals in the visual, auditory, vestibular, olfactory, and gustatory systems. On the basis of the data available to him, he concluded that in all special sensory systems specialized epithelial cells are associated with a specific nerve fiber and are probably the transducing elements of the specific receptor. His assessment of the problem in relation to the auditory, vestibular, and olfactory systems was correct.

Merkel's analogy to the eye (specifically to the retina) was, however, less accurate because he was unaware that the receptor cells of the rod are derived from the central nervous system. Thus, he correctly diagrammed the relationship of the rod receptor cell to the bipolar cell (hence to the ganglion cell and optic nerve) but failed to note (possibly because the neuron doctrine was not generally appreciated in 1880) that these are three discrete cells within a derivative of the central nervous system.

Merkel also erred in applying his thesis to the olfactory system because the continuity between the receptor cell and the fila olfactoria had not yet been demonstrated (see historical reviews of Graziadei [2,3]). However, Merkel clearly recognized the importance of the receptor cell in olfactory mucosa and cited Schultze (1862) as his authority. The peculiarity of the olfactory system is the fact that the central nervous system is invaded by a process derived from an ectodermal receptor cell which cannot easily be equated with a primary sensory neuron as it is in the retina [2]. Johnston has recently observed that the olfactory area receives an ingrowth of neural crest cells [4]. Views on this receptor cell may change as more studies on the neural crest and derivatives of this system produce more data. For the purposes of the present discussion, however, I agree with Merkel, that the olfactory system does have a specific receptor cell.

The other specialized sensory systems – auditory, vestibular, and gustatory – clearly have as a receptor cell a specialized ectodermal derivative which is intimately associated with a sensory nerve fiber. At this point, Merkel's question is relevant: "Warum, so fragt man billig, soll nun der fünfte Sinn, der Tastsinn, nicht auch mit den gleichen Endapparatten versehen sein?"* Using this argument, Merkel documented the existence of specific terminal touch cells (Tastzellen) in all known mechanoreceptors. He proposed that Tastzellen were the effective transducers of mechanical to neural information. In the rest of his monograph, Merkel documented the existence of Tastzellen in every sensory receptor in all available animals, from amphioxus to the higher phyla.

MERKEL CELLS (TASTZELLEN)

In the following discussion, I shall use the terminology proposed when I first characterized these specialized cells [5]. In 1902, Tretjakoff [6] had suggested that the specialized cell be termed a

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Abbreviations:
SA: slowly adapting

* Why, as one might reasonably ask, is only the fifth sense, that of touch, not equipped with similar terminal structure?

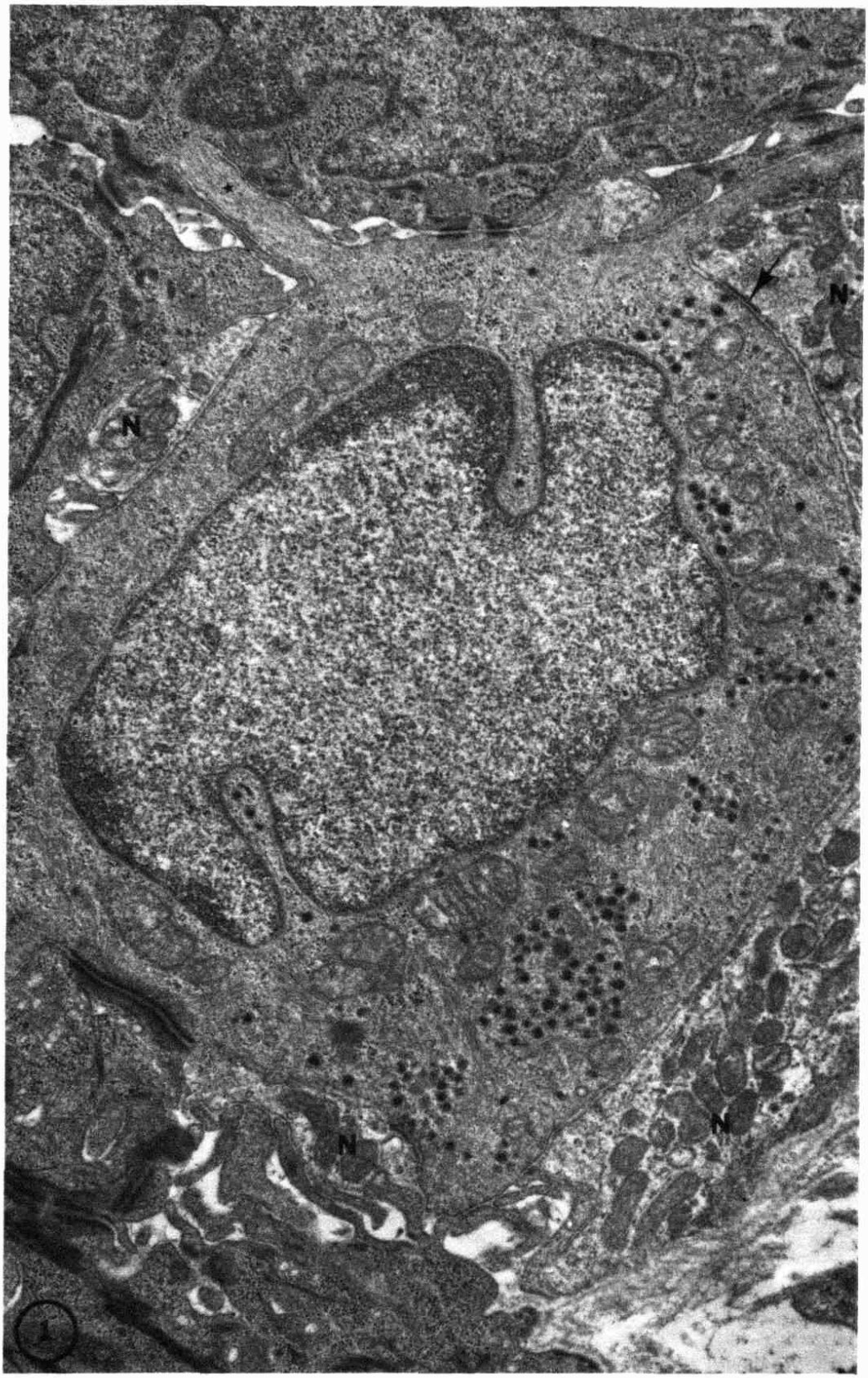

FIG. 1. Merkel cell-neurite complex in the lower lip of the rhesus monkey. The Merkel cell contains numerous electron-opaque secretory granules polarized towards an expanded profile of the associated neurite (*N*). In addition to desmosomes between the neurite and Merkel cell, asymmetric membrane densities (*arrow*) are present which involve the plasma membrane of the neurite. Numerous vesicles are present at this point in the axoplasm of the neurite. A stubby cytoplasmic spine (*star*) projects from the Merkel cell interdigitating with the processes of an adjacent epidermal keratinocytes in the upper left (× 15,700).

Merkel cell, rather than a touch cell. The Merkel cell and its associated neurite thus became the Merkel cell-neurite complexes [7] or, in Merkel's terminology [1], Tastkörperchen (touch bodies). The failure of many scholars to accept Merkel's thesis was probably due to prevalant methods of tissue fixation. Merkel demonstrated touch cells only in osmium-fixed tissue [1]. Osmium fixation provides good cytologic detail, but it precludes the successful staining of neurites with silver or methylene blue, techniques which usually call for formalin fixation. As a result, Merkel and subsequent scholars could not visualize both the terminal neurite and the specialized presumptive tactile cell simultaneously. They could see only the myelin sheath and the specific cell. Some authors [8,9] used neurofibrillar stains to verify the existence of "Merkel discs" in the epidermis, but this term refers only to the flattened expanse of the terminal neurite, not to the specialized cell.

Merkel cells, now accepted as discrete biologic entities, have been studied in various sites, and their association with physiologically defined, slowly adapting (SA) mechanoreceptors has been firmly documented [10]. At first glance, they resemble other protein-secreting cells [5] and are characterized by clearly definable secretory granules which are consistently polarized towards the nerve fiber. The hypothesis that Merkel cells are transducers of mechanical to quantal-chemical or electrical activity is only one of several reasonable assumptions about their function. However, despite numerous studies during the past decade in various animals, definitive data about the function of Merkel cells are still lacking [7,11-14].

Differences in the appearance of Merkel cells in different systems are minimal (Fig. 1). In general, they are large cells located within the basal region of the epidermis [5,7,12,15]; during aldehyde fixation, they are easily distorted so that only a characteristic empty artifact is left in paraffin sections [1]. In electron micrographs the cell contains numerous membrane-limited secretory granules measuring ~100 nm in diameter with irregular electron-opaque cores polarized towards the neurite (Fig. 1). The Golgi apparatus is opposite the side where these granules accumulate; presumptive prosecretory (newly formed) granules, however, are associated with the Golgi apparatus [5]. Since the characteristic granules seemed to me to resemble the protein secretory granules of other cellular systems, I regard them as *presumptive secretory granules*. Stubby cytoplasmic protrusions interdigitate with the processes of the surrounding epidermal cells, and desmosomes are present between the Merkel cells and the surrounding epidermal cells. Junctional complexes as well as the fusion of the specific granules with the plasma membrane of Merkel cells produce areas of membrane density [16]. I was unable to discern membrane specializations between Merkel cells and associated neurites either in the glabrous skin of the opossum snout [7] or in the glabrous digital skin of the raccoon [17]. In more recent studies, however, we consistently found membrane specializations between the plasma membrane of Merkel cells and that of the subjacent sensory neurite in primate material (Fig. 1) [18,19]. We have occasionally seen accumulations of vesicles in the neurite axoplasm as well as suggestive subsynaptic cisternae in the Merkel cells [20]. This suggests that we could be dealing with a reciprocal type of synaptic relationship, i.e., an efferent as well as an afferent relationship between the neurite and the underlying Merkel cell. Antidromic firing within the terminal branches of cutaneous nerves is possible; such a mechanism could operate especially in highly branched peripheral nerve terminals where clusters of Merkel cell-neurite complexes are present, e.g., in Haarscheiben or Merkel rete papillae [17,20].

MERKEL CELL-NEURITE COMPLEXES (TASTKÖRPERCHEN)

We have occasionally identified isolated Merkel cells, apparently lacking an associated sensory nerve fiber, within the epidermis or other epithelial systems, but most often Merkel cells are seen as a complex of specialized cells and a subjacent, closely applied nerve terminal. We refer to such complexes as Merkel cell-neurite complexes [7,12].

The system which best exemplifies clusters of these complexes that have been morphologically and physiologically verified is the Haarscheiben [21]. First described and documented in the hairy skin of the cat [10], Haarscheiben are also found in the hairy skin of the rat [22] and of nonhuman and human [23] primates. Because these clusters of Merkel cell-neurite complexes are seen as distinct protrusions from the skin surface, they were called *touch domes* by Iggo and Muir [10]. These receptors are clearly SA mechanoreceptors [7,10,12, 13,15,24]. The presence of Merkel cell-neurite complexes in vibrissae or sinus hairs [7,12,25,26] also links Merkel cells with SA physiologic parameters.

Clusters of Merkel cell-neurite complexes are also present in the glabrous digital skin of the raccoon [17] and man [27]. We called these clusters *Merkel rete papillae* since they are not domes on the skin surface and are not associated with hairs. Similar clusters of Merkel cell-neurite complexes are present in the oral mucosa of both human and nonhuman primates [18,19,28]. In both glabrous skin and oral mucosa, these clusters protrude down into the stroma of connective tissue as "nipples" or "papillae" which protrude from the rete ridges of primate or the rete pegs of raccoon digital skin. (Note that the digital skin of the raccoon does not have rete ridges [11] but instead is organized as cylinders of epidermis (rete pegs) which protrude into a meshwork of dermal ridges). The protrusion of Merkel cell-neurite complexes from the overlying epithelium into the underlying con-

nective tissue probably accounts for the so-called "dermal Merkel cells" described by Breathnach [29] and by Winkelmann and Breathnach [11]. In our experience, these dermal Merkel cells are always the result of section artifact, i.e., serial sections show them to be continuous with the epithelium even in embryonic primate material. Working with the glabrous digital skin of the raccoon, we verified the fact that these clusters of Merkel cell–neurite complexes are SA mechanoreceptors [30] similar to the Haarscheiben or sinus hairs in hairy skin. Because of the density of these receptors in the glabrous digital skin of primates, we could not establish a precise correlation in such skin. Merkel rete papillae were always present, but so were other receptors [31].

Finally, the recent study of Pubols, Donovick, and Pubols [32] used physiologic methods to document Merkel cell–neurite complexes as SA mechanoreceptors in a still different anatomical site. In this study, numerous SA mechanoreceptors were found in the glabrous snout skin of the opossum, the site of my original ultrastructural description of Merkel cells [5]. Hypothetically, Merkel cells are cellular transducers of tactile stimuli, but data to prove this hypothesis are still lacking.

Breathnach [29] and Winkelmann and Breathnach [11] have demonstrated that Merkel cells differentiate embryologically very early (Fig. 2). I have also observed such early differentiation in cutaneous as well as oral systems during the first trimester of gestation, when the peripheral sensory nervous system is still immature. Thus, my earlier suggestion that these cells might be trophic in nature again appears reasonable [7].

A trophic relationship certainly exists between sensory nerves and Merkel cells. Palmer [33] suggested that Merkel cells in the snout skin of the opossum degenerate 3 to 4 days after section of the infraorbital nerve. This study was never published in detail. Smith [22] was unable to confirm such degeneration in the rat, but English and co-workers ([34–36] provided convincing morphologic and physiologic evidence of Merkel cell degeneration after nerve trauma and of regeneration after degeneration. The cytologic documentation of English et al supports the theory of a trophic relationship between the Merkel cell and its associated neurite. The role this relationship plays in the development and regeneration of the peripheral nervous system cannot be overemphasized.

CORPUSCULAR RECEPTORS

Corpuscular receptors consist of clusters of sensory nerve fibers closely associated with specialized lamellar cells more or less segregated from the general connective tissue compartment by capsular elements [7,12,18]. From Merkel's work [1], one could assume that Merkel cells would be present in such systems as genital end bulbs and Herbst's corpuscles.

The specialized cell common to most corpuscular receptors is a lamellar cell. We erroneously referred to this cell as a laminar cell in an earlier study [37]. These cells are a distinctive feature of many corpuscular receptors [7,12], including genital end bulbs, Herbst corpuscles, simple corpuscles, Pacinian corpuscles, and Meissner corpuscles [38–40], and have similar characteristics in the various corpuscular receptors (Figs. 3, 4). The relationship between the nerve fibers and associated epithelial cells is established through the elongated processes of the epithelial cells, the so-called cytoplasmic lamellae (Fig. 4). Thus, in many corpuscular receptors, specialized lamellar cells, thought to derive from Schwann cells [41], extend long cytoplasmic processes towards the sensory nerve fiber to establish a complex relationship that is specific for each type of corpuscular receptor.

The studies of Idé [39,42] and Saxod [41] suggest that the lamellar cells of specific sensory receptors are closely related to neural crest elements or Schwann cells [43]. There is no evidence that they originate in the connective tissue or are related to perineurium. In the absence of any criteria for defining epithelium [39], it is impossible to determine cytologically whether perineurium is an epithelial tissue. Thus, though the capsule of corpuscular receptors is thought to be perineural epithelium, it is not always possible to see a complete basal lamina [7,37,39].

Corpuscular receptors characterized by the presence of lamellar cells, e.g., Pacinian, Herbst, and simple corpuscles, have sometimes been characterized physiologically as rapidly adapting mechanoreceptors [7,12,20,24,30]. By inference, Meissner corpuscles and genital end bulbs could also be regarded as rapidly adapting mechanoreceptors. Recently I was unable to characterize individual receptors in the glabrous digital skin of squirrel monkeys because the density of Meissner corpuscles and other receptors was too great [31].

The argument that specialized cells are related to sensory nerve terminals becomes somewhat more tenuous when Golgi tendon organs [44] or Ruffini corpuscles (D. Beimesderfer, B. L. Munger, J. Binck, R. Dubner: unpublished data) are considered cytologically [18]. In these receptors, the terminal arborization of the nerve fiber and its associated Schwann cell appears to be specific and highly specialized especially in relation to its function of engulfing or encircling parallel bundles of collagen and elastic fibers. Even though the Golgi tendon lacks elastica [45] and the Ruffini corpuscle contains it, both have a similar pattern of cytologic organization [18,46, (D. Biemesderfer, B. L. Munger, J. Binck, R. Dubner: unpublished data)]. The specialized cell discussed here is not a lamellar cell but a specialization of the Schwann cell and its associated nerve fiber proper.

As the specialized interaction of terminal neurite (with Schwann cell) and a connective tissue compartment shows, these two corpuscular receptors (i.e., Ruffini corpuscles and Golgi tendon organs) are cytologically unique and are, further-

more, SA mechanoreceptors [13,18,44,47]. We can thus distinguish cytologic as well as physiologic specificity not only in intraepithelial nerve fibers but in corpuscular receptors as well.

One classically described corpuscular receptor, the Grandry corpuscle found in birds, contains cells which in many respects resemble Merkel cells. However, the functions of this receptor have not been precisely defined. Unlike all other Merkel cell neurites that are SA [48], these may be rapidly adapting. I have never been convinced that Grandry cells are Merkel cells [7,12] even though Merkel [1] contended that both corpuscular (Grandry and Herbst) receptors in birds contain similar specialized cells. Herbst corpuscles clearly contain lamellar cells in the core whereas Grandry corpuscles appear to be unique, resembling no other known sensory terminal.

SPECIAL SENSES

We propose to explore briefly the relationship between nerve fiber and sensory cell within the

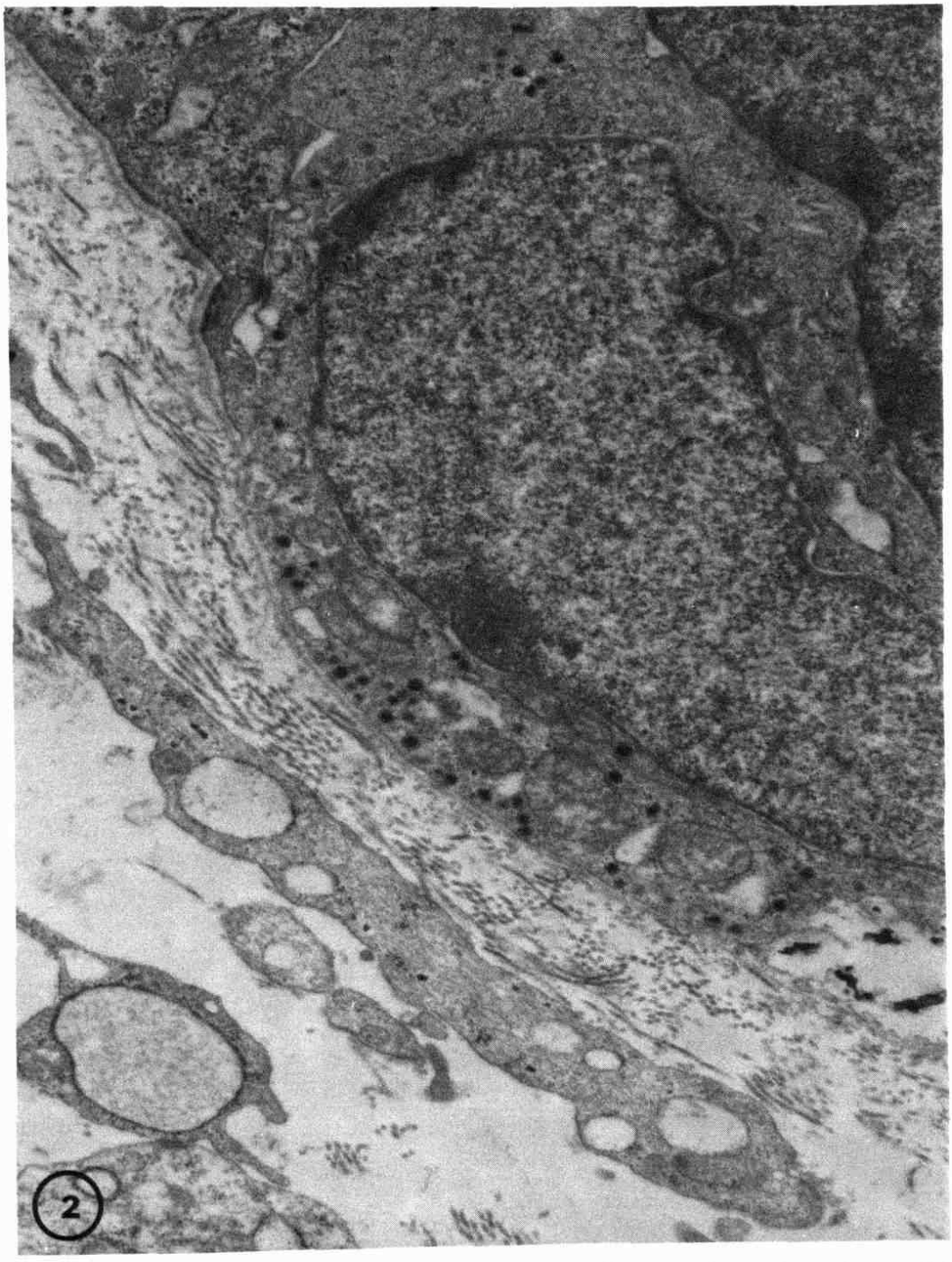

FIG. 2. An isolated Merkel cell from the upper lip of a 6- to 7-cm rhesus monkey embryo. An associated nerve fiber could not be defined in this area. The electron-opaque material in the lower right is masses of glycogen (× 7,775).

FIG. 3. A portion of a Meissner corpuscle from mouse toe pad is depicted in this micrograph by Dr. C. Idé [39]. The terminal (*UT*) portion of the sensory neurite (*N*) courses back and forth in a plane parallel to the skin surface separated by cytoplasmic lamellae derived from a lamellar cell (*L*). The terminal portions of the neurite are flattened (→←) in a plane parallel with the skin surface and at these areas have small protrusions (→). The terminals contain numerous mitochondria (*M*) and vesicles (*V*). The lamellae have a distinct basal lamina (*BL*) at the margin of the corpuscle. The myelinated nerve (*MN*) supplying this corpuscle is sectioned *at the lower left*. The capsule (*Cap*) is not complete and at the arrow (→) does not have a basal lamina, but the capsular elements are continuous with the perineurium of the nerve. A small unmyelinated neurite (*n*) is present between the corpuscle and overlying epidermis (*EP*) and the basal lamina is continuous (× 8,000). This micrograph was published in *The American Journal of Anatomy* [39] and reprinted with the permission of The Wistar Press.

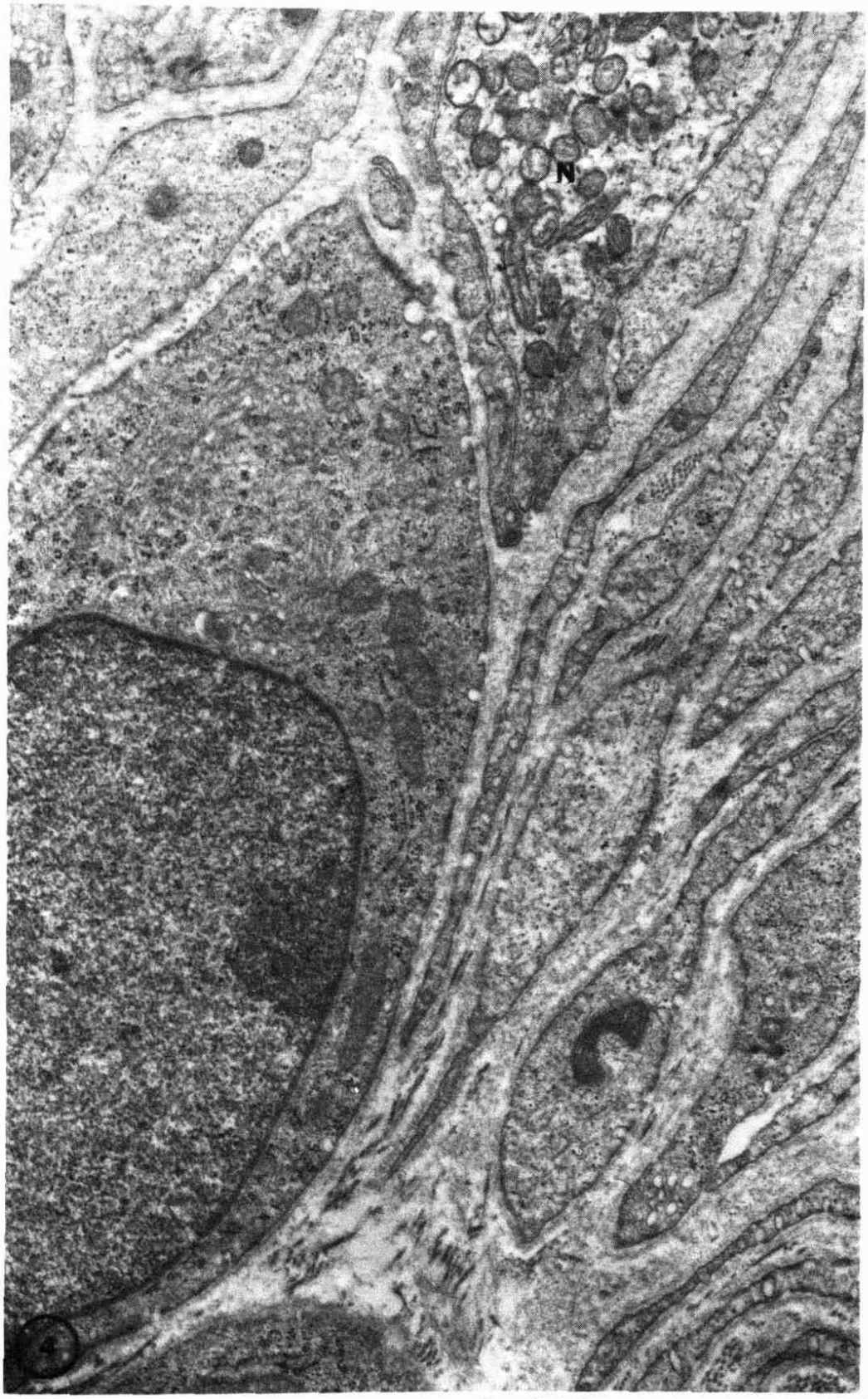

FIG. 4. A portion of a Meissner corpuscle from the tongue of an adult rhesus monkey. A portion of the lamellar cell body is depicted *to the lower left*, and numerous cytoplasmic lamellae envelop a neurite profile (*N*). The lamellar cell and the cytoplasmic lamellae are invested with a delicate layer of basal lamina. A few small bundles of collagen and numerous microfilaments are present between cytoplasmic lamellae. The cytoplasmic lamellae contain numerous pinocytotes vesicles (× 30,000).

auditory, vestibular, olfactory, and gustatory systems. We will omit the visual system since the receptor is itself a specialized neuron of the central nervous system, i.e., a true primary sensory neuron. Evidence suggests that within the auditory and vestibular systems the hair cells of most living organisms are specific receptors, i.e., the actual transducers of mechanical to electrical energy [49]. Although the nature of this process is still open to debate [50], we can assume that it occurs within the limits of the receptor cell or at least of the epithelium. Nerve fibers abutting such a cell conduct an afferent impulse away from the specific receptor towards the sensory ganglia and from there to the brain stem proper (Fig. 5). An efferent innervation has also been described in most auditory and vestibular systems (Fig. 5) [49]. The efferent innervation of hair cells has been relatively easy to define because the nature of the membrane specializations and location of membrane densities tend to differ from those of the afferent side of the receptor neurite complex.

In the auditory and vestibular systems, the afferent innervation of the receptor cell is characterized by an electron-opaque synaptic ribbon and associated synaptic vesicles in the receptor cell cytoplasm (Fig. 5). The efferent synapse usually has asymmetric membrane densities and numerous subsynaptic cisterns of endoplasmic reticulum (Fig. 5).

In mammalian chemosensory systems, which cell can be designated as the transducer or chemosensory cell is somewhat questionable. Dr. C. Idé and I have proposed that the nomenclature of chemosensory systems be changed to provide a broader definition of such systems without, however, implying a psychophysical perception of taste or smell. Olfactory mucosa is a chemosensory system and the receptor (olfactory) or chemosensory cell projects an outgrowth of its cytoplasm as an axon to extend into the olfactory bulb [2,51] (Fig. 6). Within olfactory mucosa, three cell types are present: supporting, chemosensory or receptor, and basal cells (Fig. 6). The first two are highly specialized and are most likely derived from the basal cells. According to recent evidence [2,52,53], subtle cytologic differences within the olfactory mucosa proper are partially related to differences in the life cycle of the individual cells. The renewal of the chemosensory, as well as the supporting cells, within olfactory epithelium is considerably faster than previously suspected [52]. Since the chemosensory cells extend a process into the substance of the central nervous system, i.e., to the olfactory bulb, their nerve terminals must be constantly renewed as well. Such a turnover would be a "normal" explanation for the degeneration which stains such as the Fink–Heimer technique show taking place within the olfactory bulb. Thus, in the olfactory system, the chemosensory cell as well as its axon is renewed [2,3,52,53].

In taste receptors it is difficult to characterize a specific chemosensory cell [54]. Current studies of Idé and Munger (unpublished data) on laryngeal units which resemble taste buds in structure have suggested that three cell types analogous to those in the olfactory system are present: basal cells, chemosensory cells, and sustentacular cells. We suggest that structural units anatomically similar to lingual taste buds should generally be referred to as chemosensory corpuscles. Thus, the specific receptor cells would be called chemosensory cells and the associated cells, sustentacular or supporting cells. The basal cells would be undifferentiated.

The sequence of differentiation to chemosensory or sustentacular cells in lingual taste buds involves a renewal rate similar to that in olfactory mucosa [54]. In the rhesus larynx, chemosensory cells have elaborate synaptic relationships with sensory nerve fibers (Fig. 7) which sometimes resemble the calyciform terminals seen in vestibular type I hair cell. Although the sustentacular cell indubitably makes the principal contact with the corpuscle core, we wonder whether the chemosensory cell also does not extend a single process towards the core of the chemosensory corpuscle.

The chemosensory cell in rhesus monkeys is characterized by large electron-opaque secretory granules, sometimes referred to as dense-cored granules in lingual taste buds [55,56]. These granules should be clearly differentiated from the dense-cored granules associated with the sympathetic nerve fibers which contain catecholamines. They resemble the specific granules of Merkel cells or the granules of the chemosensory or glomus cells of the carotid body [57–59]. In all of these systems, we are dealing with an extremely electron-opaque, membrane-limited unit, which can be conceptually regarded as a secretory granule or as a large dense-cored vesicle. These granules are often so closely related to the plasma membrane of the cell as to sometimes suggest a release mechanism [57,58]. This is true not only of Merkel cells, but also of the chemosensory cells of the lingual taste buds and of the carotid body. In this context, the organization of the carotid body is quite similar to that of the chemosensory corpuscles found in the larynx or tongue.

Thus, in the chemosensory cells of three different chemosensory systems (lingual taste buds, laryngeal chemosensory corpuscles, and carotid body), specific cytoplasmic organelles (secretory granules) are present which resemble those of Merkel cells. If these granules represent neurotransmittor substances, their role must be complex. The carotid body glomus cell contains catecholamines; the Merkel cell does not [5,7,22]. However, according to recent electron microscopical studies [59,60], reserpine depletes the catecholamine content of carotid body glomus cells, but not the content of secretory granules. This anomalous result would be consistent with the thesis that the specific granules represent some substance other than stored catecholamine.

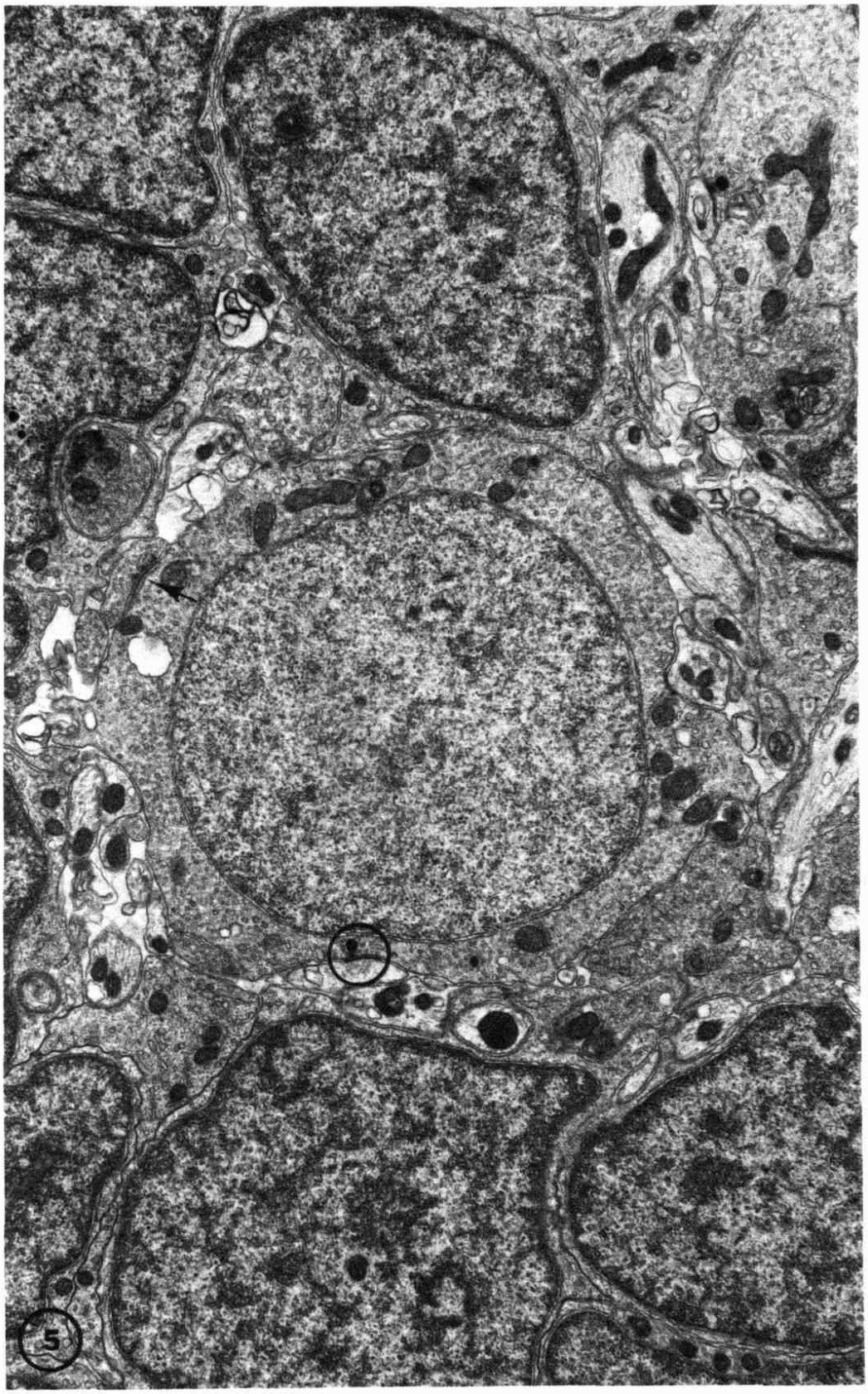

FIG. 5. This electron micrograph depicts the basal portion of a conventional (type II) hair cell from the papilla neglecta of the lizard, *Anolis carolinensis*, and was kindly supplied by Dr. Irwin Baird, Department of Anatomy, Pennsylvania State University, Milton S. Hershey Medical Center, Hershey, Pennsylvania. Several nerve endings abut the hair cell including afferent terminals (*circle*) characterized by an electron-opaque synaptic ribbon and numerous synaptic vesicles, as well as a membrane density on the neurite plasma membrane. The efferent terminals have less conspicuous membrane specializations on the neurite plasma membrane and are characterized by subsynaptic cisterns in the cytoplasm of the hair cell (*arrow*) (× 10,800).

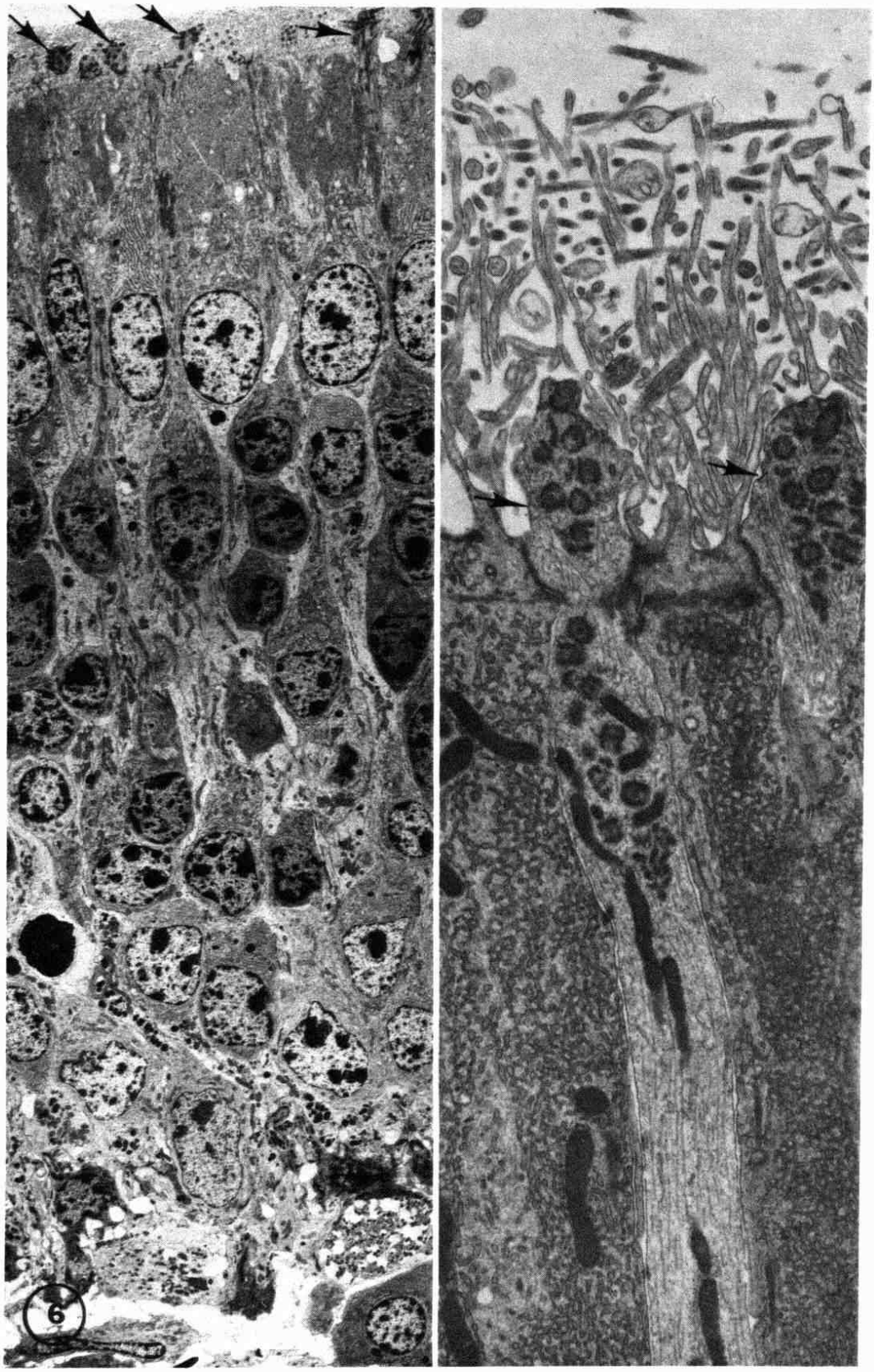

FIG. 6. These electron micrographs of rat olfactory mucosa have been kindly provided by Dr. Pasquale Graziadei, Department of Biological Science, The Florida State University, Tallahassee, Florida. The *view to the left* depicts a cross section of the entire mucosa. The chemosensory cells extend to the surface where they form expanded ciliated knobs, usually referred to as olfactory vesicles (*arrows*). The receptor terminals are seen at higher magnification in the *micrograph to the right*. The cilia of the chemosensory cell are enmeshed with numerous microvilli derived from the supporting or sustentacular cell. The cytoplasm of the supporting cell contains numerous profiles of a granular endoplasmic reticulum, whereas, the chemosensory cell contains microtubules and filaments (neurofilaments) and small clusters of granular endoplasmic reticulum (resembling Nissl bodies of other neurons) (× 1,600 and 25,000).

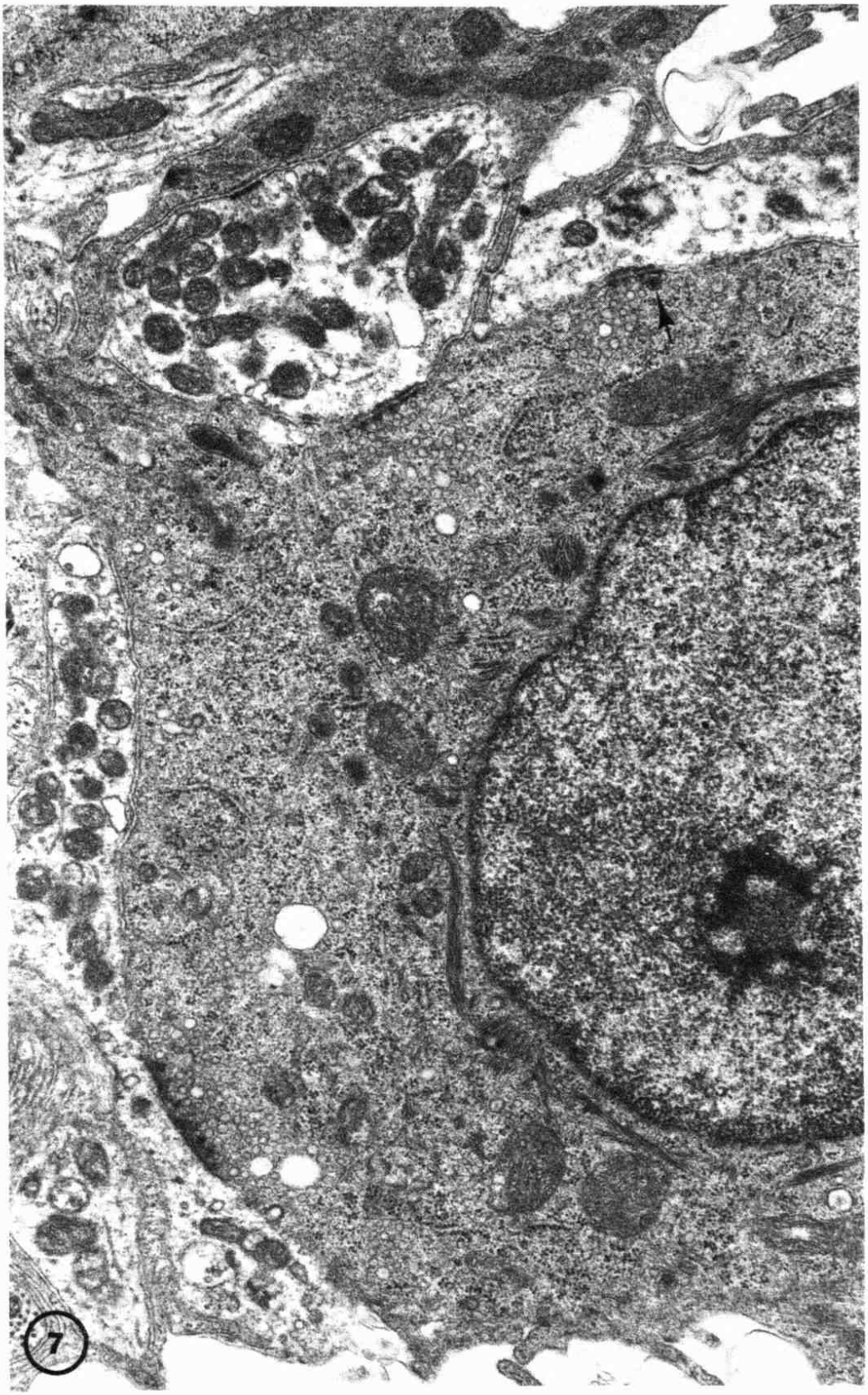

FIG. 7. A portion of a laryngeal chemosensory corpuscle from an adult rhesus monkey. The cell in the center is a chemosensory (type III) cell and has numerous synaptic contacts with surrounding nerve fiber. A secretory granule (*arrow*) is closely apposed to one of the synaptic regions (× 60,000).

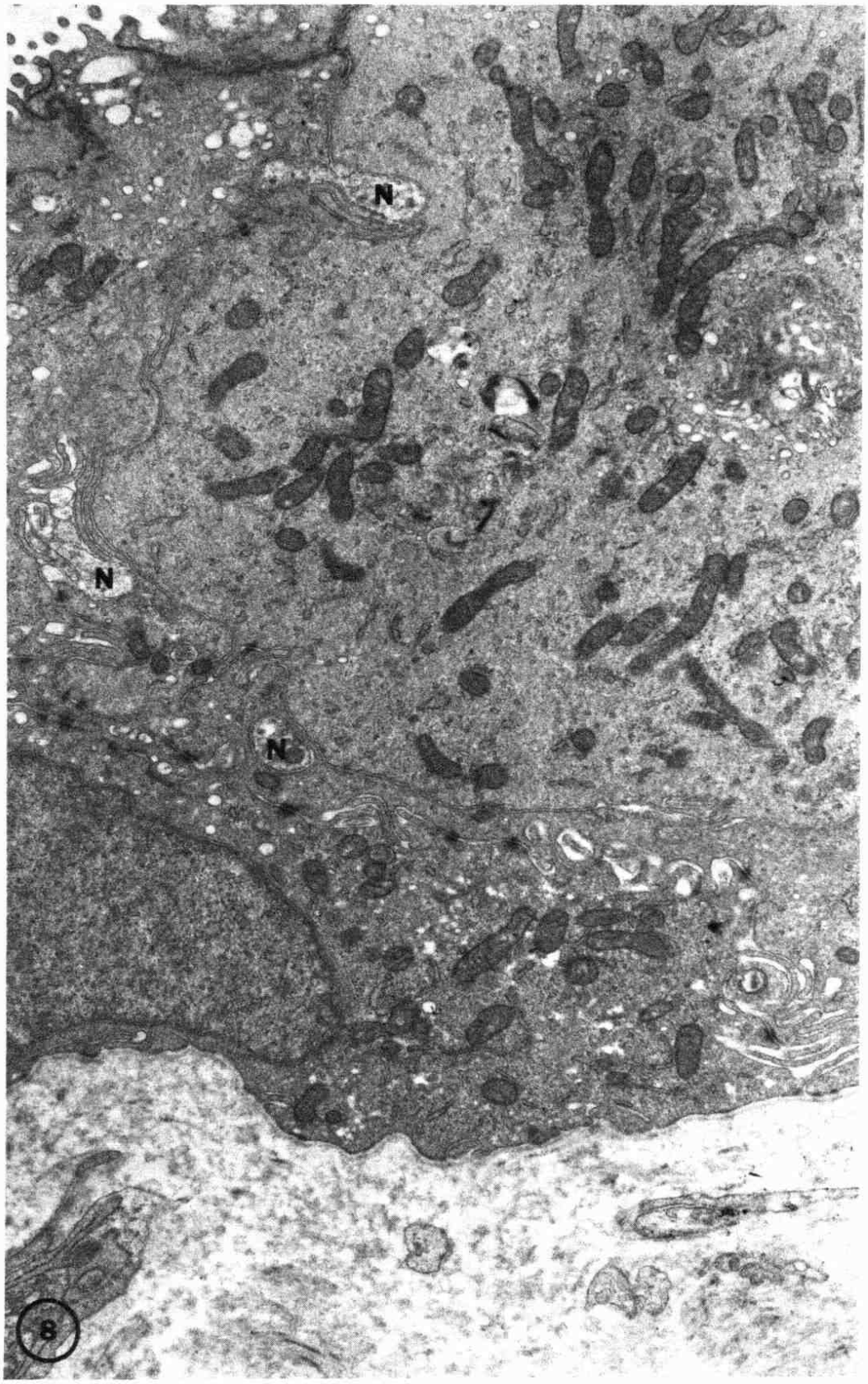

FIG. 8. The mucosa of the posterior surface of the epiglottis of an adult rhesus monkey. Several profiles of nerve fibers (*N*) course between the epithelial cells of the mucosa. A specific relationship to the epithelial cells is not evident. The airway is present *to the upper left* (× 10,200).

INTRAEPHITHELIAL NERVE FIBERS WITHOUT MERKEL CELLS

Some intraepithelial nerve fibers have no associated Merkel cells, e.g., epiglottal epithelium. Whereas our rhesus monkey material was extensively innervated, no Merkel cells were defined (Fig. 8). However, we regard this system as the exception rather than the rule. Certainly except for those associated with Merkel cells, intraepithelial nerve fibers are rarely encountered in skin [29].

CONCLUSIONS

Despite the exception, we regard the thesis, first stated by Merkel [1], as valid. The specificity of terminal neurite and associated epithelial cells provides a morphologic basis for end organ (? functional) specificity in sensory nerve terminals. Those studies which have reported only limited specificity in terminal sensory nerve endings have generally used limited cytologic criteria [60,61] to identify sensory terminals. We cannot identify all sensory receptors according to the physiologic definition provided by Horch [24], but we can identify most.

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